

# **Latent Tuberculosis Infection: A Guide for Massachusetts Providers**

Prepared by  
**The Medical Advisory Committee  
for the Elimination of Tuberculosis (MACET)**

MACET is an independent committee appointed by  
the Commissioner of the Massachusetts Department of Public Health

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## **Introduction**

In November 2000 the Medical Advisory Committee for the Elimination of Tuberculosis (MACET) undertook the task of developing guidelines that could be used in testing for and treating latent tuberculosis infection by primary care physicians and staff associated with managed care organizations. In addition, MACET developed a step-by-step quantitative approach to evaluating the effectiveness of a program for testing and treating latent tuberculosis infection.

Since that time, the Guide has been a valuable tool for clinicians throughout the Commonwealth. MACET recently revised the Guide in accordance with present day research and clinical studies.

The recommendations on testing for and treating latent tuberculosis infection in Section I are based on new national guidelines developed jointly by the Centers for Disease Prevention and Control (CDC) and the American Thoracic Society.

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## *Latent Tuberculosis Infection (LTBI) Targeted Testing and Treatment: Commonly Asked Questions and Answers<sup>1</sup>*

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<sup>1</sup> These recommendations are based on guidelines published jointly by the Centers for Disease Control (CDC) and the American Thoracic Society (ATS): Am J Resp Crit Care Med 2000;161:S221-43; MMWR June 9, 2000 Vol 49, No RR-6: 1-51, MMWR Aug 31, 2001 Vol 50, No 34, 733-735, and MMWR August 8, 2003 Vol 52; 735-739. Copies of TB-related statements published in MMWR are available through the Division of Tuberculosis Prevention and Control, MDPH (617-983-6970) and through the CDC site on the World Wide Web ([www.cdc.gov/nchstp/tb/](http://www.cdc.gov/nchstp/tb/)).

## I. Testing for Latent TB Infection

### Question 1. What is latent tuberculosis infection (LTBI)?

The term *Latent Tuberculosis Infection* (LTBI) defines an asymptomatic state in persons who are infected with *Mycobacterium tuberculosis* and have no clinical or radiographic evidence of active disease. The organism resides within the host in a clinically inactive, or latent, state, contained by the host immune response. Latent TB infection currently is detected by a standardized, intradermal skin test, termed the *tuberculin skin test* (TST), -- or by a blood test (*QuantiFERON*<sup>®</sup>), in persons with risk factors for exposure to TB. For persons with untreated latent TB infection and intact immunity, the estimated risk of developing symptomatic tuberculosis disease is 5% to 10% over a lifetime, with about 50 – 80% of that risk occurring during the first 2 years following infection. For persons who are immunocompromised by HIV co-infection, the risk of developing disease increases to 5% to 10% per year.

Active TB disease *rarely* is discovered in asymptomatic persons by tuberculin skin testing. However, finding LTBI provides an opportunity to treat and prevent reactivation of the latent infection that leads to active disease. Studies have shown that treatment of LTBI can prevent reactivation TB with an efficacy of 60%-90%. Because of the relatively low TB prevalence in the United States, and with reactivation tuberculosis representing a large proportion of new cases, treatment of LTBI is considered an important public health strategy to achieve national TB elimination. Latent TB infection generally is not treated in high-prevalence countries, because detection and complete treatment of active disease is the top personal and public health priority. One exception is children who are contacts of known cases; they are usually tested and treated even in high-prevalence countries.

### Question 2. What is the best test for LTBI, and how should test results be recorded?

Tuberculin skin testing with intermediate strength (5 TU – “Tuberculin Units”) purified protein derivative (PPD), administered by the Mantoux intradermal technique (*not by multiple puncture devices, such as Tine*<sup>®</sup> *or Mono-Vacc*<sup>®</sup>), is the current standard test for detecting LTBI. The TST is administered by injecting 0.1 ml (5 TU) PPD solution intradermally (*not* subcutaneously), usually into the ventral surface of the forearm. Forty-eight to 72 hours after the test is administered, the diameter of palpable or visible *induration* (raised swelling) is measured **transverse to the long axis of the arm (i.e. across the arm)** and recorded in mm.<sup>2</sup> Note: *redness without induration should be ignored*. Reading of the TST should be performed by a person who is adequately trained in its interpretation; patients, or parents of patients, should NEVER be permitted to read their own skin tests.

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<sup>2</sup> Three reading methods have been recommended. With one method, the arm is positioned so that a light shines tangentially over the skin reaction, highlighting any induration. The lateral edges of the visible induration are marked with a pen and measured with a millimeter (mm) ruler. With the second method, the lateral edges of the induration are determined by moving a ballpoint pen across the arm from each side until resistance is met. A mark is made and the diameter is measured with a mm ruler. The third method involves direct palpation of the induration, marking the edges and measuring the distance across the forearm. With any of these methods, only the measurement transverse to the long axis of the arm (not two dimensions) is recorded.

**Caution:** The Massachusetts Department of Public Health and others have received multiple reports of *false-positive reactions* using Aplisol<sup>®</sup> (Squibb), one of the 2 brands of tuberculin skin testing reagent currently licensed in the US. **Therefore, Tubersol<sup>®</sup> (Connaught) is the only agent recommended by MACET for tuberculin skin testing in Massachusetts.**

**QuantiFERON-Gold<sup>®</sup>** is a new test approved by the FDA for detection of latent TB infection, in certain circumstances. This laboratory test uses an ELISA to measure the production of interferon-gamma by whole blood leukocytes incubated overnight with PPD solution. It requires a single patient visit for a blood draw, and results are reported as positive or negative, based on a calculated stimulation index and on risk factors for TB exposure. Special processing of the blood and plasma by trained laboratory personnel is necessary. Following its published indications, the *QuantiFERON* test is an acceptable substitute for the TST in Massachusetts. (ref: Centers for Disease Control and Prevention. *Guidelines for using the QuantiFERON-TB test for diagnosing latent Mycobacterium tuberculosis infection*. MMWR 2003; 52(RR-2):15-18.)

### **Question 3: Who should be tested for LTBI in Massachusetts?**

Testing for LTBI should be reserved for persons who meet some or all of the following criteria:

- Are at high risk of TB infection (see Question 4).
- If infected, are at high risk of developing active TB.
- If infected, would be a candidate for treatment to prevent active TB.
- If they developed active TB, would place vulnerable contacts at risk.

### **Question 4: Who is at high risk of TB in Massachusetts today?**

High-risk persons in Massachusetts who should be tuberculin skin tested include:

- Close contacts of known active pulmonary TB cases, or persons working or residing in congregate settings (shelters, jails, and some health care facilities) considered high-risk for TB.
- Foreign-born persons from high-prevalence countries, or persons with extended (> 1 month) travel to these countries.<sup>3</sup>
- Persons with fibrotic abnormalities on chest x-ray<sup>4</sup> consistent with previous, untreated TB.
- Persons with clinical conditions associated with progression to active TB, such as HIV infection, silicosis, diabetes, chronic renal failure/hemodialysis, gastrectomy, jejunioileal bypass, solid organ transplantation (renal, cardiac), carcinoma of the head and neck, and being more than 15% underweight and who also are likely to have been exposed to TB.

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<sup>3</sup> High-prevalence places from which Massachusetts TB cases have come in recent years include, but are not limited to, China, Southeast Asia, India, Haiti, Dominican Republic, Central America, Brazil, Russia, and sub-Saharan Africa. TB case rates have almost tripled in the former Soviet Union in the decade following its dissolution, and an increasing number of cases among recent arrivals is expected.

<sup>4</sup> Prior tuberculosis disease can have a variety of nonspecific appearances. However, radiographically dense, upper lobe linear or nodular changes are characteristic. Hilar, lower lobe, and pleural densities are also seen, but are less specific for TB. For example, in the Ohio River Valley, hilar calcifications are more likely to represent previous histoplasmosis than TB. Apical pleural thickening without parenchymal scarring is specifically not associated with TB.

- Injection drug users.
- Children who meet these criteria or who have been in regular contact with high-risk adults with LTBI also are considered at risk (see footnote 7). This is not to suggest that persons with LTBI are themselves infectious, but they may indicate other, active, infectious persons in the environment.
- Immunocompromised persons (e.g. HIV, chronic corticosteroid use, administration of TNF- $\alpha$  inhibitors or receptor blockers) with risk(s) for TB exposure.

Note: *In the ATS/CDC Guidelines referenced on p. I-1, Tables 2 and 3 indicate risk estimates for these and other factors. Note: We have developed a questionnaire that can be used in clinical settings to help determine a child's risk of tuberculosis and the need for a tuberculin skin test (Appendix 1).*

**Question 5: Should persons who have been vaccinated with BCG (*bacille Calmette-Guerin*) be tested for LTBI, and if tested, how should the results be interpreted?**

*Bacille Calmette-Guerin* (BCG) is administered to more than 80% of children in the world as part of the Extended Program on Immunization. The vaccine is given primarily in countries with rates of LTBI much higher than those found in the US or Western Europe, and many persons who have previously received BCG also may have LTBI. Reactions to the TST following BCG vaccination may range from no induration to  $\geq 10$  mm, although many are in the 5-9 mm range. These reactions generally wane with time, though their size can be affected by the age at vaccination, the number of vaccinations, and the number and frequency of subsequent tuberculin skin tests since vaccination. Persons who have received BCG should be tested for LTBI as clinically indicated; positive test results in persons who have had contact with a case of TB or who come from a country with a high rate of TB should be assumed to be due to TB infection, *not* BCG, and treatment should be recommended, unless contraindicated. A rule of thumb states that TST reactions of 15 mm or greater are likely to be TB, as are reactions of 10 mm or greater in persons immunized more than 15 years ago.

**Question 6: Which persons, if they develop active TB, pose an especially high risk to the community?**

Persons with active TB who may threaten the public's health include anyone with infectious TB (usually pulmonary and/or laryngeal TB) who is working or living in a congregate setting with vulnerable persons, such as HIV/AIDS or otherwise-immunocompromised patients, the elderly, homeless persons, newborn babies, and children 4 years of age and under.

**Question 7: What tuberculin skin test (TST) induration diameter is considered indicative of TB infection?**

Three cut-off points define ranges of reaction size for a positive TST: 5 mm, 10 mm, or 15 mm, depending on the risk of TB infection or disease in the individual or population being tested, as detailed below.

- **5 mm or greater TST induration:** is considered positive *only* in persons at the highest risk for infection or active disease. In this group, detecting all TB infections is considered

more important than the risk of including some false positive reactions. Four high-risk subgroups are included:

- *Close contacts* of active pulmonary or laryngeal cases.
- *HIV-immunocompromised persons* (the risk of progression to active TB, if TB infected, is 5% to 10% per year).
- *Organ transplant recipients or other immunosuppressed persons* (including persons receiving long-term, high dose oral or parenteral corticosteroid therapy (arbitrarily defined as  $\geq 15$  mg prednisone, or equivalent, daily for 1 month or longer). *Note:* Inhaled corticosteroid use is not associated with sufficient suppression of the immune system to reduce the TST response.
- Persons with *fibrotic chest x-ray findings* consistent with old TB.
- **10 mm or greater TST induration:** Such tests are considered positive for persons known to be at high risk for infection or disease. Included in this group are
  - *Foreign-born persons* from high-prevalence countries (see footnote 3).
  - *Disadvantaged low-income persons* (malnutrition, crowded housing, medically underserved).
  - Persons *over age 70* and children *4 years of age and under*.
  - Persons residing or having resided for extended periods in *congregate settings* known to be associated with TB transmission, such as shelters, jails, prisons, and detoxification or drug-rehabilitation centers.
  - Injection drug users.
  - *Health care workers and other workers* in facilities serving populations at increased risk of unsuspected TB disease, or engaged in high-risk procedures such as bronchoscopy, sputum induction, autopsies, mycobacteriology laboratory work, or work in homeless shelters.<sup>5</sup>
  - Other high-risk professions, such as mortuary work.<sup>6</sup>
- **15 mm or greater TST induration:**
  - Persons at low risk of TB infection, for whom TST is generally not indicated, are more likely to have false-positive reactions if a 10 mm cut-off is used, due to non-specific hypersensitivity to environmental mycobacteria. It has been estimated that as many as 3 out of 4 TST indurations of 10 mm to 14 mm in low-risk persons are not due to TB. By increasing the cut-off size to 15 mm in low-risk persons, sensitivity decreases but specificity increases. The mean induration diameter for persons with culture-positive tuberculosis in Massachusetts is 17 mm. In contrast, only 3% of non-anegetic TB cases persons have reactions of less than 10 mm induration. Low-risk persons with TST results less than 15 mm induration should not be considered TB-infected; they should be retested only if their risk status changes. Most schoolchildren in Massachusetts, unless they have specific risk factors for TB, should no longer be routinely tested for TB.<sup>7</sup>

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<sup>5</sup> Health care facilities and other Massachusetts workplaces covered under OSHA regulations should follow current OSHA directives regarding TST testing, interpretation, and treatment.

<sup>6</sup> Out-of-date local or state regulations have required food-handlers, hairdressers and other workers not at increased risk to be tested for TB. Ideally, testing should be avoided, but if required, the 15 mm cut-off should be used unless other risk factors apply. The Massachusetts law mandating pre-employment tuberculin skin testing for all school personnel was repealed in 2003.

<sup>7</sup> Tuberculosis testing of schoolchildren should be based on individual risk factors (see Question 4), not the location of their school or residence. MACET has developed a questionnaire (see Appendix 1) to assist pediatricians determine which children should be tested. Copies are available through the Massachusetts Department of Public Health, Division of Tuberculosis Prevention and Control (617-983-6970).

**Question 8. Who should be retested for LTBI in Massachusetts?**

Only those with *ongoing risk of exposure to TB* should be retested. In a low-prevalence state like Massachusetts, relatively few people are included in this category. Close contacts of known, infectious TB cases, persons likely to be exposed by travel in high-prevalence regions of the world, and persons who work at jobs associated with exposure (some health care workers, shelter workers, correction officers, *etc.*) should have repeat testing, at a frequency determined by the estimated risk, or by regulations, such as those issued by institutions or by the Occupational Safety and Health Administration (OSHA).

**Question 9. Can repeat skin testing for TB cause a positive reaction?**

No. The administration of a tuberculin skin test cannot, by itself, cause reactivity to future tuberculin skin testing in persons who have not been infected with TB. However, repeated skin testing can cause the false impression of recent infection (TST conversion) in persons who had actually been infected in the remote past.

In the absence of subsequent stimulation, TST reactivity wanes over a period of many years following TB infection. This fading of “immune memory” for the antigens in PPD may give a falsely-negative result following the administration of a single TST years after the initial infection. However, the host’s immune memory for PPD can be *boosted* by the first TST after many years, so that the subsequent TST reaction size may be significantly larger than on the initial test, even if no further exposure to TB has occurred. The repeat TST in such cases thus may appear to have *converted* from negative to positive. However, the *boosted* reaction does not reflect *recent* infection; rather, it represents stimulated immune memory for past infection. In persons who are to undergo serial tuberculin skin testing (as may be required in some circumstances, such as for high-risk employees of certain health care facilities; see Question 10, below), using a *2-step baseline skin test* procedure and using a *change in induration of 10 mm as criteria for conversion*, are recommended steps to minimize boosting and the incorrect diagnoses of skin test conversions. See *Screening for Tuberculosis and Tuberculosis Infection in High-Risk Populations. Recommendations of the Advisory Council for the Elimination of Tuberculosis* (MMWR 44:18-34, September 8, 1995; <http://www.cdc.gov/mmwr/preview/mmwrhtml/00038873.htm>) for further discussion.

**Question 10. What is 2-step tuberculin skin testing, and when is it indicated?**

False TST conversions due to *boosting* of waning hypersensitivity to the antigens contained in PPD (see Question 9) can be reduced by administering a 2-step baseline skin test – in those increasingly uncommon circumstances when repeated TB skin testing is indicated by the high risk of ongoing infection (*e.g.*, some health care workers). This applies only to person who have not received a TST in the recent past (*i.e.* this may be defined arbitrarily within a period of years long enough for immunity to wane – 5 to 10 years, for example). It is generally not required for young people, arbitrarily those under age 20, for example.

Procedure:

1. Administer the first TST, as usual.

2. If the first TST is positive (according to the above risk-based criteria), the subject is considered TB-infected, and further skin testing is not warranted.
3. If the first TST is negative, a second TST is done (one week to one month later) and, again, it is read at 48-72 hours. This second reading may be larger than the first (a 10 mm change is considered significant), due to boosting. If positive, the subject is considered TB-infected and evaluated for LTBI treatment. If still negative, this second test becomes the **baseline** measurement (*i.e.* mm induration) against which future skin test results are compared.
4. On subsequent testing, an increase in reaction size of 10 mm or more from the baseline reaction is considered a true conversion (*i.e.* indicating infection has occurred since the previous TST), and should warrant evaluation for active disease. If active disease is not found, treatment of LTBI should be considered.

## II. Treatment of Latent TB Infection

### Question 11: Who should be treated for latent TB infection?

Anyone at high risk for TB who has a positive tuberculin skin test for TB infection is a candidate for treatment, if they also fulfill the following criteria:

- No symptoms, signs, or radiographic evidence of active TB.<sup>8</sup>
- Willing to complete a full course of therapy (treatment of LTBI is not mandatory, even if strongly recommended).
- Available to be clinically monitored by a health care provider during the full course of treatment.
- No medical contraindications to treatment, such as severe liver disease, drug hypersensitivity, or medical conditions that make adherence unlikely, such as mental illness or alcoholism. *Where available, supervised treatment (also called directly observed treatment, or DOT) can increase adherence for high-risk persons.*

### Question 12: What are the currently recommended treatments for LTBI?

In the past, only isoniazid (INH) was recommended for treatment of LTBI, but now there are 3 treatment options, 1 of which is rifampin-based and does not include INH:

Option 1. INH daily (self-administered or supervised), or twice-weekly (supervised), for 9 months

- Considered the optimal treatment in terms of efficacy.
- May be limited by its long duration (may discourage initial acceptance and long-term adherence) and its potential for hepatotoxicity, especially for persons over age 35 years.<sup>9</sup>

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<sup>8</sup> In the absence of symptoms suggesting pulmonary or extrapulmonary TB, only the history, physical examination, and chest x-ray should be part of a clinical work-up for LTBI. Other tests, such as sputum or urine culture, have an extremely small yield, and are subject to false-positive results if done routinely. The erythrocyte sedimentation rate (ESR) is neither sensitive nor specific for active TB.

<sup>9</sup> INH hepatotoxicity is age-related, with increasing rates over age 35 years. (See Question 15).

- Recommended for children<sup>10</sup> and adults, with or without HIV co-infection, and with or without fibrotic chest x-ray abnormalities suggesting old TB.

Option 2. INH daily (self-administered or supervised), or twice-weekly (supervised) for 6 months

- Considered sub-optimal compared to the 9-month INH treatment because it is less effective.
- Advantages over the 9-month INH treatment: Greater initial acceptance and long-term adherence may be more likely, and marginally less hepatotoxicity than the 9-month regimen. Potential for hepatotoxicity increased for those over age 35 years (see footnote 9).
- Recommended for adults without HIV co-infection and without chest x-ray abnormalities suggesting old TB.

Option 3. Rifampin alone for 4 months.

- Efficacy considered comparable to the 6-month INH treatment, but few studies have examined the efficacy of rifampin as a single agent for the treatment of LTBI (refs: Hong Kong Chest Service, Tuberculosis Research Centre, Madras, and British Medical Research Council. 1992. A double-blind placebo controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am. Rev. Respir. Dis.* 145:36—41; Polesky A. Farber HW. Gottlieb DJ. Park H. Levinson S. O'Connell JJ. McInnis B. Nieves RL. Bernardo J. Rifampin preventive therapy for tuberculosis in Boston's homeless. *Am J Respir Crit Care Med.* 154:1473-7, 1996).
- Shorter duration than INH; less hepatotoxicity.
- Limited by potential interactions of rifampin with many other medications, including birth control pills and hormonal implants<sup>11</sup> and anti-retroviral therapy used for HIV/AIDS.<sup>12</sup>
- Rifampin may cause false-positive urine test for opiates, which may be an important consideration in cases involving some types of workers who may be subject to routine testing (such as bus drivers or law enforcement personnel).
- Useful option for INH -intolerant adults or for contacts of known INH-resistant cases. A recent review strongly suggests wider use of this regimen because of its short duration and safety (Reichman, LB, Lardizabal, A, Hayden, CH. Considering the role of four

Months of rifampin in the treatment of latent tuberculosis infection. *Amer J Respir Crit Care Med.* 170:832-5, 2004.)

***NOTE: The recommendation for a 2 month regimen of rifampin plus pyrazinamide (2RZ), originally made in the April, 2000, ATS/CDC Guidelines, has been withdrawn because of its unacceptably high rate of hepatotoxicity. The 2 month rifampin plus pyrazinamide***

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<sup>10</sup> INH for 9 months is the only regimen recommended for treatment of children with LTBI at this time.

<sup>11</sup> An alternative method of birth control (e.g. a barrier method, such as condoms) must be used by heterosexually-active women to avoid pregnancy.

<sup>12</sup> Interactions between rifamycins and drugs used in HIV treatment are complex (see Question 15).

**regimen should not be used in either HIV-negative or HIV-positive persons for treatment of LTBI (MMWR 52(31), 735-739, August 8, 2003).**

### **Question 13: How do I decide which treatment regimen to choose for my patient?**

Choosing a treatment regimen is based on several considerations, such as

- **Efficacy:** All 3 treatments are considered efficacious, although the 9-month INH regimen is considered more efficacious than either 6-month INH or the 4 month rifampin.
- **Medical considerations:**
  - Active liver disease, history of previous hepatitis, or factors predisposing to liver disease such as alcoholism, injection drug use, and use of prescription drugs associated with liver toxicity: postpone or reconsider therapy. Rifampin is associated with less hepatotoxicity than INH.
  - Essential medications that interact with rifampin (including HIV therapy, see footnote 12): avoid rifampin, postpone, or reconsider treatment.
  - Birth control pills and hormonal implants: avoid rifampin or find alternative birth control (*e.g.* barrier method, such as condoms).
  - Pregnancy: INH and rifampin are considered safe (category C) during pregnancy, when necessary; vitamin B6 is recommended with INH during pregnancy. Close monitoring for hepatotoxicity during pregnancy and for at least 3 months postpartum is warranted in women treated for LTBI. Many providers and patients prefer to postpone elective treatment for LTBI until after pregnancy on the general principal that none essential drugs should be avoided, especially during the first trimester. However, HIV infection and recent TB exposure with TST conversion are strong indications for therapy during pregnancy.
  - Breast feeding: not a contraindication to therapy. Although drugs may be secreted in breast milk, no adverse effects from these drugs on nursing infants have been demonstrated.
- **Logistical considerations:** Persons who will be moving from the area or who are in a supervised setting for a limited duration (*e.g.* college students, detox, rehabilitation, prison) may be more appropriate for a shorter regimen. Persons who can be supervised over a longer period (*e.g.* in prisons) may be given the 9-month INH treatment regimen with less fear of non-adherence.
- **Age:** Risk of INH-induced hepatitis increases with age (see footnote 9). Previous ATS/CDC recommendations limited INH to persons under age 35 years; for persons older than 35 years of age, treatment was recommended only when other risk factors, such as recent TST conversion, HIV co-infection, or x-ray abnormalities suggesting old TB, were present. The *current* ATS/CDC recommendations assume that only high-risk persons are tested, and therefore, treatment with INH and /or rifampin is warranted at any age. In reality, however, considerable administrative testing (required for job clearance, immigration, etc) still occurs among persons at low-risk for TB. Of the 3 approved treatment regimens for LTBI, 4 months of daily rifampin alone may have the least hepatotoxicity for those over age 35.
- **Cost:** INH is less expensive than rifampin alone. However, shorter course regimens generally require fewer office visits (see Question 15: *Monitoring*, below). Drug intolerance, drug interactions, and laboratory tests are among the other costs to be

considered. In Massachusetts, treatment for LTBI is available free of charge through the Massachusetts Department of Public Health’s TB clinic system.

- **Patient choice:** In the absence of factors dictating one regimen or another, patients often have strong opinions about taking one INH tablet daily for 6 or 9 months, or 2 rifampin capsules daily for 4 months. Current preparations of INH in suspension are based in sorbital, and at doses indicated for older children and adults can cause diarrhea.

**Question 14: What are the appropriate dosages for the 3 LTBI treatment options, and how should they be prescribed?**

The dosages are listed below. Please refer to the official CDC/ATS guidelines for additional details (Table 8, ATS/CDC LTBI Statement, AJRCCM 2000).

- **INH: (50, 100, 300 mg tablets; 50 mg/5 ml oral suspension)**
  - Adults: 5 mg/kg (300 mg, max) daily, or 15 mg/kg (900 mg, max) twice weekly.
  - Children: 10-20 mg/kg (up to 300 mg) daily, or 20-30 mg/kg twice weekly (up to 900 mg) twice weekly (see response to Question 13, above, *re.* INH suspension and diarrhea).
- **Rifampin: (150, 300 mg capsules)** 10 mg/kg (600 mg, max) daily or twice weekly (unlike twice weekly INH, dose is not increased). Not recommended for treatment of LTBI in children.
- **Rifabutin:**<sup>13</sup> **(150 mg capsules)** 5 mg/kg (300 mg max) daily or twice weekly (rifabutin daily or twice weekly is reduced to 150 mg when used in combination with indinavir).

**Question 15: How should I monitor safety and adherence during LTBI treatment?**

Regular monitoring of treatment for LTBI is performed for 3 purposes: to reinforce patient education, to encourage adherence, and to increase safety. Recommended monitoring varies with the 3 regimens:

- **INH (9- and 6-month regimens):** Monthly visits to a trained health care provider are strongly recommended during INH therapy. It is the standard-of-care for all Massachusetts TB clinics. Patients are given a prescription for no more than a one-month drug supply, and this prescription is re-filled following each monthly clinical assessment. The main complications of INH therapy are:
  - *Hepatitis.* In patients taking INH, hepatitis occurs with increasing frequency with age. In over 11,000 patients receiving INH in a public health clinic, Nolan reported a hepatitis rate of only 0.1% among patients; the majority of patients in this study were under age 35 years (JAMA 1999 281; 1014-18. Full text available at: <http://jama.ama-assn.org>). Only clinical monitoring for symptoms and signs suggestive of hepatitis (loss of appetite, fatigue, malaise, nausea, RUQ abdominal discomfort, fever, dark urine, jaundice) was used in this study. Hepatitis was confirmed by liver function tests. All patients recovered with prompt cessation of the drug.
  - Most patients can be followed without baseline or routine follow-up liver function tests *if* they are educated appropriately and can be closely monitored clinically and

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<sup>13</sup> Rifabutin may be substituted for rifampin in HIV/AIDS patients who are being treated with some anti-retroviral therapy regimens (see Question 15).

questioned at least monthly about symptoms. *With the onset of any new symptoms, patients should be clearly instructed to first stop INH and then call their provider for further instructions. The rare fatalities associated with INH hepatitis have been associated with continued INH ingestion, despite hepatitis symptoms.* Indications for baseline and periodic biochemical monitoring include patients over age 35 or with known abnormal liver function, known liver disease, or a history of hepatitis or factors that predispose to hepatitis, such as alcoholism, injection drug use, and use of prescription drugs associated with hepatitis, including prior liver toxicity from INH. Up to 20% of people who receive INH will experience mild, asymptomatic elevations in serum transaminases. INH should be stopped when transaminase elevations exceed 5 times normal in the absence of symptoms, or 3 times normal if symptoms suggestive of hepatitis are present.

- *Peripheral neuritis.* Uncommon among patients taking daily isoniazid (5 mg/kg/day) who are not receiving supplemental pyridoxine (vitamin B6). However, vitamin B6 (10-50 mg daily) is recommended for pregnant women and for anyone whose intake of vitamin-rich foods is questionable (e.g., alcoholics). Most public health TB clinics do not routinely prescribe pyridoxine, in an effort to keep treatment as simple as possible.

- **Rifampin:** Although rifamycins have been associated with a wide range of side effects, including hepatitis, neutropenia, and a flu-like syndrome, these complications are not common. Compared to INH, rifampin causes less hepatitis and has the best safety profile of the major anti-tuberculous agents. However, rifampin and other rifamycins induce hepatic microsomal enzymes and often accelerate metabolism of other important drugs, including methadone, birth control pills and hormonal implants, coumadin, some antihypertensives, and many others. The mutual interactions of protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and rifamycins is discussed in detail in a recent CDC announcement available on the internet at [http://www.cdc.gov/nchstp/tb/tb\\_hiv\\_drugs/toc.htm](http://www.cdc.gov/nchstp/tb/tb_hiv_drugs/toc.htm). (see footnote 5).

In general, no (NOTE, ATS does recommend baseline CBC and platelets) baseline or routine biochemical or hematologic monitoring is recommended for persons who are receiving rifampin, but the performance of other therapeutic agents should be monitored during and after rifampin therapy. Should symptoms develop, biochemical or hematologic testing is indicated. Monthly clinical monitoring is recommended for the 4-month rifampin regimen.

### **Question 16: How much treatment of LTBI can be missed before the patient must start over?**

This question applies to all 3 regimens. Ideally, patients should take the equivalent of the entire treatment course, even if additional time is needed due to interruptions. Some clinical judgment is needed, since clinical trial data are not available to support the efficacy of the countless possible patterns of drug ingestion. For the 9-month INH regimen, at least 270 doses should be ingested within 12 months. For the 6-month INH regimen, at least 180 doses should be ingested within 9 months. Finally, for the rifampin regimen, at least 120 doses should be administered within 6 months. With any regimen, clinical re-evaluation is indicated for interruptions of greater than 2 months. In patients who demonstrate non-adherence where DOT is not indicated or available, treatment should be restarted only once and then re-evaluated if non-adherence re-

occurs. The indications for LTBI treatment are important factors in deciding how many treatment attempts are warranted in each case.

**Question 17: If a patient will not or cannot take treatment for LTBI, what is appropriate follow-up?**

Patients who cannot, or will not, take treatment for LTBI generally are *not* followed clinically for development of active TB. *Neither periodic clinical exams nor periodic chest x-rays has been shown to be effective in detecting TB disease(reactivation tuberculosis) before symptoms develop, and neither is recommended.* Patients should keep a record of their positive TST and understand its significance. Patients should be instructed to seek medical care if they develop signs and/or symptoms of active TB, such as an unexplained cough that lasts more than 2 weeks, and to remind their provider of their positive TST status. Patients who complete a course of treatment for LTBI require no further follow-up and should be given a record of their status. *"Routine," periodic chest x-rays are not indicated in the absence of signs or symptoms of active TB.*

**Question 18: When should I seek consultation with a specialist?**

Primary care providers are encouraged to request consultation with a pulmonary or infectious disease specialist with experience in tuberculosis management, for the following reasons:

- Treatment of LTBI in pregnancy.
- Treatment of LTBI in patients receiving complex therapy for HIV.
- Treatment of LTBI or active TB when drug resistance is likely (contact of a known drug-resistant case).
- Diagnosis and management of active TB, including interpretation of mycobacteriology laboratory data.
- TB drug complications and interactions.
- Cultural/ethnic, or other barriers to TB prevention are identified.

### **III. Public Health Aspects**

**Question 19: Is LTBI reportable to the health department?**

Latent TB Infection now is reportable to the state health department in Massachusetts. *The LTBI Reporting Number (by Fax) is 617-983-6990.* Reporting forms can be obtained from the Massachusetts Department of Public Health Division of TB Prevention and Control.

Active TB patients and patients suspected of active TB also are reportable by law, even if a final diagnosis of TB is yet not established. Cases and suspect cases are reported by telephone to the Massachusetts Department of Public Health Division of TB Prevention and Control 24 hours daily by calling 1-888-MASSMTB (1-888-627-7682).

**Question 20: What public health resources are available to my patients and me?**

The Massachusetts Department of Public Health Division of Tuberculosis Prevention and Control, in cooperation with local health departments, provides comprehensive care for persons with TB in Massachusetts. Nineteen clinics in health care facilities across the state offer medical expertise, radiography, mycobacteriology, and TB therapy free of charge to the patient for both LTBI and disease. Contact investigations of infectious cases, source case investigations, patient and family education, hospital discharge planning, and directly observed therapy are essential public health services provided by the Department of Public Health. For active TB cases, case management is the shared responsibility of the treating physician and the local and state public health nurses, and, if necessary, the support of culturally-targeted outreach educator staff. For LTBI, initial evaluation, medications, and essential laboratory monitoring are provided. Consultation for private physicians treating cases of active TB and LTBI is another service of the Massachusetts Department of Public Health. Dr. John Bernardo, the State Tuberculosis Control Officer, can be reached at 617-983-6970 (State TB Prevention and Control Program), 617- 339-7281 (pager), or by email: [jbernardo@lung.bumc.bu.edu](mailto:jbernardo@lung.bumc.bu.edu).

## **Appendix 1: Tuberculosis Risk Questionnaire**

The Tuberculosis Risk Questionnaire appears on the following page. It can be reproduced for distribution as needed.

## **Appendix 2: Treatment of Latent Tuberculosis Infection Reference Card**

The Treatment of Latent Tuberculosis Reference Card appears on the following page. It can be reproduced, folded, and distributed as needed.

### **Appendix 3: Evaluation of Program Performance**

The primary purpose of tuberculosis skin testing of healthy children and adults is to identify those with latent infection whose future risk of active disease can be reduced by preventive treatment. Preventing active tuberculosis also decreases the risk of the spread of tuberculosis to others. The prospect of tuberculosis elimination will be enhanced.

In order to be effective, a program of testing and treatment of latent tuberculosis infection (LTBI) requires completion of a number of steps, and the success of each step can be defined by a quantitative performance measure. Each office, health center, and clinic should maintain its own statistics that can serve as the basis for monitoring and continually improving performance. Statistics should be calculated every three months and annually. These statistics should be available for inspection by the Massachusetts Department of Public Health.

At some future time, a tuberculosis performance measure might be added to current Health Plan Employer Data and Information Set (HEDIS) parameters used to assess the quality of preventive health care, such as childhood immunization, Pap smear, and mammogram rates.

#### **Step 1: Identify People at High Risk for Tuberculosis Infection**

Risk of exposure to tuberculosis should be determined for every patient on entry into the health care system and at regular intervals thereafter. Depending on circumstances, a health care provider may decide to determine risk of tuberculosis exposure through individual clinical history taken or by administering a formal tuberculosis risk questionnaire (Section I, Appendix 1). Definition of risk categories should be according to the recommendations of the Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the Massachusetts Department of Public Health.

##### *Performance Measure*

$$\text{Proportion Screened} = \frac{\text{Number of People Screened for Tuberculosis Risk}}{\text{Number of People Seen}}$$

#### **Step 2: Test People at High Risk for Tuberculosis Infection**

The Mantoux test (intermediate PPD), (5 TU), not multiple puncture tests (such as Tine and Mono-Vacc), must be used.

*Performance Measure*

$$\text{Proportion Tested} = \frac{\text{Number of High Risk People Tested}}{\text{Number of High Risk People Identified}}$$

**Step 3: Read Skin Test Results**

All tests results, positive or negative, must be read by qualified health care personnel. Tests should be read between 48 and 72 hours after administration. The diameter of induration, not redness, is the basis of the reading. Test results should be measured in millimeters and interpreted as “positive” or “negative” according to the criteria recommended by the Centers for Disease Prevention and Control, the American Academy of Pediatrics, and the Massachusetts Department of Public Health.

*Performance Measure*

$$\text{Proportion of Tests Read} = \frac{\text{Number of Tests Read}}{\text{Number of People Tested}}$$

**Steps 4: Obtain Chest Film for People with Positive Tuberculosis Skin Tests**

People with a positive tuberculosis skin test should have a medical evaluation and chest film. A chest film is needed to distinguish latent tuberculosis infection from active disease.

*Performance Measure*

$$\text{Proportion of People with Positive Tuberculosis Skin Test} = \frac{\text{Number of Positive People Who have Chest Films}}{\text{Number of People with Positive Tests}}$$